1605
H-022B

OSHA HAZARD COMMUNICATION PROPOSAL

USWA POST-HEARING SUBMISSION
AUGUST 31, 1982

EXHIBITS S-1 THROUGH S-4

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF CARCINOGENIC RISK
OF CHEMICALS TO MAN

Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics

VOLUME 11

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
LYON
1976

Exhibit 5-1

1,4-DIOXANE*

1. Chemical and Physical Data

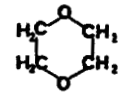
1.1 Synonyms and trade names

Chem. Abstr. Reg. Serial No.: 123-91-1

Chem. Abstr. Name: 1,4-Dioxane

Diethylene dioxide; 1,4-diethylene dioxide; diethylene ether; di(ethylene oxide); 1,4-dioxacyclohexane; dioxan; 1,4-dioxan; *para*-dioxan; dioxane; *para*-dioxane; dioxyethylene ether; glycol ethylene ether; tetrahydro-1,4-dioxin; tetrahydro-*para*-dioxin

1.2 Chemical formula and molecular weight



$C_4H_8O_2$ Mol. wt: 88.1

1.3 Chemical and physical properties

(a) Description: Colourless, inflammable liquid

(b) Boiling-point: 101.1°C

(c) Melting-point: 11.8°C

(d) Density: d_4^{20} 1.0329

(e) Refractive index: n_D^{20} 1.4175

(f) Solubility: Miscible with water, organic solvents, aromatic hydrocarbons and oils

(g) Volatility: Vapour pressure is 37 mm at 25°C.

---

*Considered by the Working Group, February 1976

(h) Stability: Stable to light but forms explosive peroxide in air, especially in the presence of moisture

(i) Reactivity: Reacts with oxygen to form peroxide

1.4 Technical products and impurities

1,4-Dioxane is available in the US in reagent, technical, spectrophotometric and scintillation grades (Hawley, 1971). The technical grade is more than 99.9% pure. Specifications for a typical commercial product are: peroxides (as H_2O_2), 50 mg/kg max.; acidity (as acetic acid), 0.01% by weight max.; water, 0.1% max.; 2-methyl-1,3-dioxolane, 0.05% max.; and non-volatile matter, 0.0025% max. This grade is substantially free from suspended matter (Anon., 1970a).

Specifications for 1,4-dioxane produced in Japan are: purity, 99.99%; boiling-point range, 101-102°C; freezing-point, 11.7°C; density d_4^{20}, 1.0333; and refractive index n_D^{20}, 1.4224. Water is present as an impurity.

2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p. 19.

2.1 Production and use

1,4-Dioxane can be prepared by: (1) the dehydration of ethylene glycol (believed to be the commercial route) (Anon. 1962); (2) the treatment of bis(2-chloroethyl)ether with alkali (Hawley, 1971); or (3) the dimerization of ethylene oxide (Rowe, 1963).

Commercial production of 1,4-dioxane in the US was first reported in 1951 (US Tariff Commission, 1952); production in 1972 was 6.3 million kg (US Tariff Commission, 1974) and in 1973, 7.4 million kg (US International Trade Commission, 1975). There are four companies now producing this compound in the US.

In 1972, three Japanese companies were manufacturing 1,4-dioxane (Anon., 1972a), and another was completing a plant with a capacity of 2.2 million kg per year (Anon., 1972b). In 1968, 600 thousand kg were produced, and in 1973, 2.3 million kg. Japan exported 60-70 thousand kg of 1,4-dioxane in 1974 and about 100 thousand kg in 1975, chiefly to the UK and Australia.

In the US, 1,4-dioxane is used mainly as a stabilizer in chlorinated solvents; in 1973, it was estimated that future growth for this purpose would be 7-8% per year (Anon., 1973). It is also used as a solvent for cellulose acetate, ethyl cellulose, benzyl cellulose, resins, oils, waxes, oil and some dyes (Stecher, 1968), and as a solvent for electrical, agricultural and biochemical intermediates and for adhesives, sealants, cosmetics, pharmaceuticals, rubber chemicals and surface coatings (Anon., 1970b).

The major uses of 1,4-dioxane in Japan are as a solvent, as a surface-treating agent for artificial leather and as a stabilizer for trichloroethylene.

Permissible levels for 1,4-dioxane in the working environment have been established in various countries (Winell, 1975). The threshold limit value in the US is 360 mg/m^3 (100 ppm) and the maximum allowable concentration in the USSR is 10 mg/m^3.

2.2 Occurrence

No data were available to the Working Group.

2.3 Analysis

White *et al.* (1970) used activated-charcoal traps and subsequent gas chromatographic analysis to determine solvent vapours in industrial atmospheres; the same procedure in combination with mass spectrometry was used by Cooper *et al.* (1971). Conditions for separation of a number of solvents, including 1,4-dioxane, by gas chromatography are given by Grupinski (1966). Gas chromatography/mass spectrometry has also been used to determine 1,4-dioxane in water samples (Harris *et al.*, 1974). Reio (1970) used paper chromatography to separate and identify several compounds including 1,4-dioxane. Limits of detection by gas chromatographic methods were of the order of 0.3 µg/l of air.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Mouse: No tumours occurred in groups of 50 male and 50 female B6C3F1 mice administered 0.5 or 1% 1,4-dioxane in the drinking-water for 40-43 weeks (King *et al.*, 1973) [The short duration should be noted].

Rat: A group of 26 male Wistar rats was given 1% 1,4-dioxane in the drinking-water for 63 weeks (total dose, 130 g). Liver tumours, ranging from small neoplastic nodules to multifocal hepatocellular carcinomas, occurred in 6 animals. In addition, 1 rat developed a transitional-cell carcinoma of the kidney pelvis, and 1, a leukaemia. One lymphosarcoma occurred in 9 controls (Argus *et al.*, 1965).

Four groups of 28-32 male Sprague-Dawley rats were given 0.75, 1.0, 1.4 or 1.8% 1,4-dioxane in the drinking-water for 13 months (total doses, 104-256 g/animal) and killed after 16 months. One rat receiving 0.75%, 1 receiving 1.0%, 2 receiving 1.4% and 2 receiving 1.8% 1,4-dioxane developed tumours of the nasal cavity; these were mainly squamous-cell carcinomas, with areas containing adenocarcinomas in 2 cases. Liver-cell tumours (hepatomas and hepatocellular carcinomas) developed in 3 rats receiving 1.4% and in 12 rats received 1.8%. Microscopic lesions described as 'incipient hepatomas' were observed in all treated groups. A subcutaneous fibroma occurred 'on the back of the nose' in 1/30 controls (Argus *et al.*, 1973; Hogh-Ligeti *et al.*, 1970).

Four groups of 60 male and 60 female Sherman rats were given 0, 0.01, 0.1 or 1% 1,4-dioxane in the drinking-water for up to 716 days (daily doses: males, 0, 8-12, 59-113, 914-1229 mg/kg bw; females, 0, 18-20, 130-160, 1416-2149 mg/kg bw). The 50% survival time at the highest dose was 16 months, compared with 22 months in other groups. At the highest level 10 hepatocellular carcinomas, 2 cholangiomas and 3 squamous-cell carcinomas of the nasal cavity were observed, compared with 1 hepatocellular carcinoma in a rat receiving 0.1% 1,4-dioxane. No statistically significant increase in the incidence of tumours was seen in rats given the two lower dose levels (Kociba *et al.*, 1974).

Guinea-pig: Twenty-two male guinea-pigs received drinking-water containing 0.5-2% 1,4-dioxane, such that normal growth was maintained, over 23 months (total dose, 588-623 g/animal). All animals were killed within 28 months. Two animals had carcinomas of the gall bladder, and 3 had hepatomas. No liver tumours were reported in 10 untreated controls (Hogh-Ligeti & Argus, 1970).

(b) Inhalation and/or intratracheal administration

Five groups of 96 male and 96 female Wistar rats were exposed either to air or air containing 0.4 mg/l (111 ppm) 99.9% pure 1,4-dioxane for 7 hours/day on 5 days/week for 2 years. Fifty per cent of the animals survived 20-24 months. No statistically significant increase in the incidence of tumours was observed in the 525 treated rats examined compared with 347 controls (Torkelson *et al.*, 1974).

(c) Skin application

Mouse: Groups of 30 male and 30 female Swiss-Webster mice received thrice weekly paintings of 0.2 ml of an unspecified concentration of 1,4-dioxane in acetone on the clipped dorsal skin for 60 weeks; 1 skin sarcoma and 1 malignant lymphoma were observed. In similar groups of mice, skin paintings were preceded 1 week earlier by application of 50 µg 7,12-dimethylbenzanthracene (DMBA); 4 males and 5 females survived the 59 weeks of treatment. Among 15 mice examined, 8 skin tumours were observed (2 papillomas, 2 squamous-cell carcinomas, and 4 sarcomas); in addition, 24 other tumours (mainly malignant lymphomas and lung tumours) occurred. Eight skin papillomas and 1 malignant lymphoma occurred in 55 animals receiving 50 µg DMBA followed by thrice weekly paintings with acetone alone (King *et al.*, 1973) [The increase in the incidence of skin tumours was significant in the 2-stage skin carcinogenesis experiment ($P<0.01$)].

3.2 Other relevant biological data

(a) Experimental systems

The i.p. LD_{50} of 1,4-dioxane in male Sprague-Dawley rats was 5.6 g/kg bw (Argus *et al.*, 1973). The oral LD_{50}'s in mice, rats and guinea-pigs were 5.7, 5.2 and 3.9 g/kg bw, respectively (Laug *et al.*, 1939). In mice,

rats, guinea-pigs and rabbits subjected to repeated 1.5-hour exposures to 3600 mg/m^3 (1000 ppm) 1,4-dioxane in air (total exposures, 78-202.5 hours), vascular congestion of the liver and degenerative changes in the renal cortex were observed (Fairley *et al.*, 1934).

In male rats given single oral doses of 10, 100 or 1000 mg/kg bw ^{14}C-1,4-dioxane, excretion of unchanged 1,4-dioxane in expired air was 0.043 mg/kg bw (0.43%) at the lowest dose and 252 mg/kg bw (25%) at the highest dose (Young & Gehring, 1975).

(b) Man

Exposure of 12 volunteers to a concentration of 1080 mg/m^3 (300 ppm) 1,4-dioxane vapour in air for 15 minutes produced irritation of the eyes, nose and throat (Silverman *et al.*, 1946).

Five acute deaths due to 1,4-dioxane exposure have been reported; haemorrhagic nephritis and liver necrosis were recorded at autopsy (Barber, 1934). Another death, in a worker, probably attributable to one week's exposure to about 1800 mg/m^3 (500 ppm) 1,4-dioxane, has been reported. There was also a possibility of skin absorption, since 1,4-dioxane was used as a solvent to remove glue from hands. Autopsy revealed damage to kidneys, liver and brain (Johnstone, 1959).

3.3 Observations in man

No data were available to the Working Group.

4. Comments on Data Reported and Evaluation[1]

4.1 Animal data

1,4-Dioxane is carcinogenic in rats and guinea-pigs by oral administration: it produced malignant tumours of the nasal cavity and liver in rats and tumours of the liver and gall bladder in guinea-pigs. It was also active as a promoter in a two-stage skin carcinogenesis study in mice. No carcinogenic effect was observed in one inhalation study in rats.

---

[1]See also the section 'Animal Data in Relation to the Evaluation of Risk to Man' in the introduction to this volume, p. 17.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

Second Annual Report on

Carcinogens

December 1981

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

PURSUANT TO SECTION 301(b)(4)
PUBLIC HEALTH SERVICE ACT
AS AMENDED BY SECTION 262, PUBLIC LAW 95622

PREPARED BY NATIONAL TOXICOLOGY PROGRAM

Exhibit S-2

1,4-DIOXANE

1,4-Dioxane is carcinogenic in rats and guinea-pigs by oral administration: it produced malignant tumours of the nasal cavity and liver in rats[1-4] and tumours of the liver and gall bladder in guinea-pigs.[3] It was also active as a promoter in a two-stage skin carcinogenesis study in mice.[5,6]

---

[1]M.F. Argus, J.C. Arcos and C. Hoch-Ligeti. Studies on the Carcinogenic Activity of Protein-Denaturating Agents: Hepatocarcinogenicity of Dioxane. J. Nat. Cancer Inst. 35:949-58, 1965.

[2]M.F. Argus, R.S. Sohal, G.M. Bryant, C. Hoch-Ligeti and J.C. Arcos. Dose-Response and Ultrastructural Alterations in Dioxane Carcinogenesis. Influence of Methylcholanthrene on Acute Toxicity. Europ. J. Cancer 9:237-43, 1973.

[3]C. Hoch-Ligeti, M.F. Argus and J.C. Arcos. Induction of Carcinomas in the Nasal Cavity of Rats by Dioxane. Brit. J. Cancer 24:164-67, 1970.

[4]R.J. Kociba, S.B. McCollister, C. Park, T.R. Torkelson and P.J. Gehring. 1,4-Dioxane. I. Results of a 2-Year Ingestion Study in Rats. Toxicol. Appl. Pharmacol. 30:275-86, 1974.

[5]M.E. King, A.M. Shefner and R.R. Bates. Carcinogenesis Bioassay of Chlorinated Dibenzodioxins and Related Chemicals. Environm. Hlth. Persp. 5:163-70, 1973.

[6]IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 11. IARC, Lyon, France, pp. 247-56, 1976.

1,4-Dioxane is a highly volatile liquid that is flammable and moderately explosive.

1,4-Dioxane is used as a stabilizer for chlorinated degreasing solvents and as a solvent for lacquers, plastics, varnishes, paints, dyes, fats, greases, waxes, and resins. It can occur as a contaminant in detergents, shampoos, and related products, and is an inevitable byproduct of reactions based on condensing ethylene oxide (or ethylene glycol).

The first commercial production of dioxane in the United States was in 1951. Currently, the EPA reports that there are 13 producers and importers accounting for 7.7 million lb of domestic production and approximately 800,000 lb of imports. No significant change in the estimated trends for U.S. production and sales of dioxane is forecast.

Exposure to dioxane is primarily through inhalation of the vapors. Dioxane is also readily absorbed through the skin. Exposure to dioxane in industry occurs when vapors are released from degreasing operations and the disposal of spent solvents. Workers also may be exposed when dioxane is formed during the manufacture of detergents, surfactants, and certain

pharmaceuticals. 1,4-Dioxane is produced in small amounts as a result of ethylene oxide condensations. Inhalation of dioxane will be trivial compared to potential inhalation of ethylene oxide (EtO). The chemical is shipped primarily by rail and truck; and workers involved with this operation may be exposed, particularly through leakage from bulk loading lines. The Consumer Product Safety Commission (CPSC) reports that consumers may be exposed to residual levels of 1,4-dioxane because it is a potential byproduct in chemical reactions using ethylene oxide. EtO is used in the production of ingredients found in fabric softeners, and laundry, hand, and dishwater detergents. A CPSC contractor has reported that it is possible but unlikely that some dioxane-stabilized 1,1,1-trichloroethane might be sold to consumer aerosol producers. The presence of 1,4-dioxane, even as a trace contaminant, is cause for concern. However, data showing the actual levels of impurities in final products and the potential for consumer exposure and uptake are currently lacking. The National Occupational Hazard Survey estimates that 334,000 workers are potentially exposed to dioxane, 100,000 of whom are exposed as a result of dioxane contamination of 1,1,1-trichloroethane. OSHA estimates that 466,000 workers are potentially exposed.

Because of its volatility and its infinite solubility in water, there is a large potential for dioxane to be present in the environment. Emissions to the atmosphere can occur where it is manufactured and used. Improperly disposed spent solvents can contaminate ground and surface waters.

The EPA regulates dioxane through the Resource Conservation and Recovery Act. The FDA has undertaken a survey of 1,4-dioxane contamination of raw materials and products. OSHA has adopted a permissible exposure limit of 100 ppm or 360 mg/m^3 as an 8-hour time-weighted average in the workplace for dioxane. This standard was adopted by OSHA for toxic effects other than cancer.

REGULATIONS

Regulations and Other Actions	Effect of Regulations and Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste product, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		FR 45.42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FD&CA: Proposed action pending; may propose to minimize its exposure.		21 CFR 175.105 (FDA)
Regulatory Authority: FD&CA 601(a). (FDA)	Survey of raw materials and product contamination underway. (FDA)	
PEL: 100 ppm (360 mg/m^3) 8-hr TWA. Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1952: Walsh-Healy, 100 ppm maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

Exhibit S-3 #150-81

TESTIMONY ON OSHA's PROPOSAL FOR GENERIC STANDARDS ON CARCINOGENS

P. J. Gehring, D.V.M., Ph.D.
Toxicology Research Laboratory
Health and Environmental Research
Dow Chemical U.S.A.

Thus, we must conclude that alkylation of DNA may lead to cancer induction. Further, we must conclude that administration of high doses inhibits or exceeds the capacity of the repair mechanism. Indeed, the data I have presented on ENU and DMN indicate that cancer occurs only if the target tissue has a poor capacity for repair of DNA or if the doses are of sufficient magnitude to inhibit repair or exceed the capacity of the repair process.

The model does not establish that low exposures to chemicals found to be carcinogenic to animals at high doses is absolutely safe. "Absolute safety" is both unrealistic and ludicrous. As indicated earlier "overnutrition" causes more human cancer than any other identifiable cause. Extrapolating those data, and introducing preventive measures consistent with absolute safety, would certainly reduce drastically the incidence of cancer--starvation would predominate!

Dose-Dependent Carcinogenesis: Detoxification (1,4-Dioxane)

Further elucidation of our model can be obtained by reviewing animal and human data from studies on 1,4-dioxane.

Studies by Kociba et al, (1974) demonstrated a small increased incidence of hepatomas and nasal carcinomas in rats maintained on drinking water containing sufficient dioxane to provide doses exceeding 1000 mg/kg/day. This dose is more than enough to produce death in some rats and marked pathology of the liver and kidneys in all. At 100 mg/kg/day, rats exhibit hepatic and renal damage but no tumors. No untoward effects were discernible in rats receiving 10 mg/kg/day. Since humans exposed to the current American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 50 ppm (180 mg/m^3) for 6 hours received a total dose of 5.4±1.1 mg/kg (Young, et al, 1977), the relevance of toxicological data obtained at doses more than one hundred-fold greater was questionable. Consequently, the applicability of toxicological responses induced in rats by large doses to assess the potential untoward effects of low doses was examined by characterizing the fate of 1,4-dioxane as a function of dose.

Metabolic Fate as a Function of Dose - Figure 10 shows the plasma concentration time-curves for rats given single intravenous doses of ^{14}C-dioxane ranging from 3 to 1000 mg/kg. The clearance of dioxane from plasma is markedly dose-dependent and in accordance with Michaelis-Menten kinetics.

The area under the curve increases disproportionately with dose indicating that, indeed, the elimination of dioxane is a saturable, dose-dependent or nonlinear kinetic process.

The chemobiokinetic model which described best the data was a parallel combination of Michaelis-Menten and first-order elimination. For this combination the apparent volume of distribution, the maximum velocity, the Michaelis constant and the apparent first-order rate constant were, respectively V_d = 301±41 ml; V_m = 13.3±1.1 µg/ml/hr; K_m = 20.9±2.0 µg/ml, and k_e = 0.0149±0.0015 hr^{-1}. The maximum capacity for elimination of dioxane by the rat is 4003 µg/hr.

Thus, a dose of 1000 mg/kg to a 250 g rat exceeds 62 times the maximum capability of the rat to eliminate dioxane per hour.

Demonstration of Dose Dependency - The excretion of ^{14}C-activity by rats given various doses of ^{14}C-dioxane also demonstrated dose-dependent kinetics; as the dose was increased, more dioxane per se was eliminated via exhalation; at low doses essentially all was excreted rapidly as beta-hydroxyethoxyacetic acid (HEAA) in the urine. Thus, the biotransformation of 1,4-dioxane to the detoxification product, HEAA, is a saturable process which is overwhelmed

by increasing the magnitude of the dose. The marked retention of dioxane with an increasing dose led us to conclude that the metabolism of dioxane must be "induced" markedly with repeated daily doses. "Induced" means that an adaptation occurs whereby the capacity to metabolize dioxane is increased.

Figure 11 shows the body burden of radioactivity in rats given repeated daily oral doses of 10 or 1000 mg/kg for 17 days. The body burden was calculated by subtracting the total cumulative excretion by all routes from the total cumulative dose and expressing the results as a percentage of the total cumulative dose. The body burden in rats given 10 mg/kg/day dioxane averaged about 5 percent and ranged between 2 and 9 percent with no apparent upward or downward trend. However, a striking decrease occurred in body burden of rats given 1000 mg/kg/day dioxane during the first four days of administration. This indicates that a dose of 1000 mg/kg/day caused a marked induction of the elimination of dioxane; 10 mg/kg/day did not cause induction. In plain language the metabolism of rats receiving 1000 mg/kg/day dioxane had markedly changed. Their responses to dioxane, whether toxicological or carcinogenic, are not extrapolatable to rats receiving low doses.

Induction of a greater capacity to metabolize a foreign compound has itself been shown to increase tumorigenesis. Peraino et al (1973a), demonstrated an enhancement of tumorigenesis in mice given 0.05% phenobarbital a well known inducer of metabolism in their diet. This induction of metabolism in rats by phenobarbital also enhanced tumor production by 2-acetylaminofluorene (2AAF), a known hepatic carcinogen (Peraino, et al, 1973b), suggesting that induction may enhance the expression of tumors by naturally occurring carcinogens.

Metabolic Fate at Occupational Exposure Levels - There was obviously a need to determine if occupational exposure levels of dioxane induced metabolic alterations. In order to assess the potential hazard incurred by inhalation of dioxane, rats were exposed to 50 ppm dioxane for 6 hrs. After 6 hrs of exposure a steady-state level of 7.3 µg/ml had been attained in plasma. Following exposure, the rate of elimination of dioxane from plasma was equivalent to that observed after low intravenous doses of dioxane, $t_{1/2}$ = 1.01 hr. Thus, this level of exposure, 50 ppm, had not saturated the detoxification mechanism for dioxane metabolism had not been altered.

To assist extrapolation of animal toxicological data to man, four human volunteers were exposed to 50 ppm dioxane for 6 hrs (Young et al, 1977). The concentration of dioxane and its metabolite HEAA in plasma during and following exposure is shown in Figure 12. During exposure, a steady-state level was obviously attained. Subsequent to exposure, the elimination of dioxane was apparent first-order kinetics having a $t_{1/2}$ of 1.0 hr^{-1}. As in the rat, essentially all of the dioxane inhaled by volunteers was eliminated as HEAA in the urine. Using the amount of HEAA excreted in the urine to estimate the total dose received, it was further determined that a human exposed to 50 ppm dioxane actually receives (on a per kg basis) about one-thirteenth the dose received by a rat exposed to the same concentration. Thus, for a material readily absorbed upon inhalation and metabolized such as dioxane, data from rats provide a 13-fold safety factor.

The simulated plasma concentration of dioxane versus time is shown in Figure 13 for repeated exposures to 50 ppm dioxane. Note that even upon repeated exposure, the levels of dioxane attained will not saturate the capability for detoxification and elimination.

Using the chembiokinetics data together with the toxicological data, it is possible to conclude that in rats adverse effects are encountered only when doses of dioxane supersede those which can be detoxified readily without induction of morphological and biochemical changes. It is highly significant that exposure of rats to 111 ppm dioxane, 7 hrs/day, 5 days/week for 2 years causes no untoward effects (Torkelson et al, 1974). In rats, this level of exposure provides a daily dose on a per kg basis 30-fold greater than that which will be received by a man exposed continuously to 50 ppm for 6 hr. Since people exposed to 50 ppm dioxane readily detoxify dioxane, it is highly unlikely that this level of exposure will be associated with untoward effects.

Dose-Dependent Carcinogenesis: Formation of a Reactive Metabolite in Risk Assessment (Vinyl Chloride)

Some chemicals require activation to a toxic form to elicit their toxic effect. Activation to the toxic form as well as deactivation of the toxic form may occur via a saturable metabolic process. For instance vinyl chloride metabolism does not increase proportionally with increasing concentrations of exposure, Table 1, (Watanabe et al, 1976a and 1976b). Rather, the amount of VC metabolized during 6 hours of exposure to various concentrations appeared in accordance with Michaelis-Menten kinetics as described by the equation:

$$v = \frac{V_m S}{k_m + S}$$

Exhibit S-4

POST-HEARING BRIEF

of

AMERICAN FEDERATION OF LABOR

and

CONGRESS OF INDUSTRIAL ORGANIZATIONS

and

UNITED STEELWORKERS OF AMERICA

AFL-CIO·CLC

on

OSHA'S
PROPOSED STANDARD ON THE IDENTIFICATION,
CLASSIFICATION AND REGULATION OF TOXIC
SUBSTANCES POSING A POTENTIAL OCCUPATIONAL
CARCINOGENIC RISK

DOCKET #H-090

October 24, 1978

815 16th Street, N.W.
Washington, D.C. 20006

> Similar evidence is available from studies of female mice and dogs, in which oophorectomy at young ages significantly reduces the incidence of spontaneous mammary cancer (Heston 1975).
>
> The fact that ovarian hormones are endogenous and required for normal physiological activity of several target tissues does not, therefore, preclude a concurrent contribution to the cancer incidence without demonstrable no-effect or threshold levels.
>
> (Ex. 224D)

Thus the carcinogenicity of several essential trace elements and natural hormones does not indicate that a threshold for cancer induction exists for these or any other substances.

7. Chemobiokinetics

The most detailed and sophisticated defense of the concept of practical thresholds was made by Dr. Perry Gehring of Dow Chemical (Ex. 4-150). Gehring correctly states that the threshold question cannot be resolved by direct dose-response experiments. However, metabolic experiments may help elucidate the shape of the dose-response curve for low doses. Gehring points out that carcinogenesis is a multi-stage process, and that the ultimate fate of a carcinogen is governed by many factors, including absorption, excretion, activation, detoxification, and other biochemical alterations. Transformed DNA is subject to various repair mechanisms. In addition, transformed cells

are subject to attack by the immune surveillance system. Gehring goes on to argue that these phenomena are characterized by Michaelis-Menton kinetics, in which the slope of the dose response curve is dependent on the dose. For example, high doses may overwhelm normal detoxification mechanisms. Molecules may compete for binding sites. Body stores of substances required for metabolic alterations, like glutathione, can be exhausted. Active transport mechanisms across cell membranes can be saturated. Thus, the response of the organism at low doses may be qualitatively different from the response at high doses. Gehring argues that carefully designed "chemobiokinetic" experiments using experimental animals may, then, help us determine the dose at which it is extremely unlikely that any individual would develop cancer. He illustrates his model by applying it to two examples -- 1, 4-dioxane and vinyl chloride. Gehring estimates that 50 ppm is a safe level for dioxane and that 1 ppm of vinyl chloride could be expected to result in no more than 1 - 5 cases of angiosarcoma per 100 million exposed workers.

Few would question the value of Gehring's work for a theoretical understanding of the metabolism of carcinogens. But there are grave difficulties in using it to predict the risk to human beings. As Dr. Gehring himself admitted, many substances can affect the metabolism of other substances:

> MR. WRIGHT: Let me ask you whether one agent can affect the renal transport of another agent.

DR. GEHRING: By all means. In fact, one of the principles of Michaelis-Menton kinetics, if you recall I think in the same document it points out that competitive inhibitors, the use of competative inhibitors is one indication that you do have that effect.

MR. WRIGHT: Precisely, thank you. You also used the example of conjugation with glutathione and indicated that there is a point at which you begin to suffer glutathione depletion and at that point you shift into a different part of the Michaelis-Menton curve.

DR. GEHRING: Yes.

MR. WRIGHT: And there are agents -- let me rephrase that. There are, are there not, many agents which can cause the depletion of glutathione?

DR. GEHRING: Many.

MR. WRIGHT: In fact, benzene is one of those which is used occasionally at Dow. There are a number of chemicals which are used at Dow which can --

DR. GEHRING: Yes. There are many things in the diet, in fact, that will do it.

MR. WRIGHT: Of course. Thank you. Although you did not use conjugation with glucuronide as an example, the situation is the same for that, isn't it?

DR. GEHRING: That is true, too.

MR. WRIGHT: Thank you. Let us get into the induction of enzymes, and you indicated in your example of 1,4 dioxane that 1,4 dioxane is an inducer of the enzyme system. I assume you meant the mixed function oxidase system, is that correct?

DR. GEHRING: That is correct.

MR. WRIGHT: Thanks. There are other things which can induce the mixed function oxidase system.

DR. GEHRING: Most of them.

MR. WRIGHT: As a matter of fact, some of those things are made a Dow, for example, chlorodioxins, which are not intentionally made at Dow, but they are a contaminant of some of your products.

DR. GEHRING: Yes. Eating a steak, eating cabbage will also do it....

MR. WRIGHT: One of the things you indicated in your paper as a reason for believing in Michaelis-Menton kinetics is the competition for active sites, and certainly, active sites can be overwhelmed by a number of different agents.

DR. GEHRING: That is correct.

MR. WRIGHT: Correct. I do not want to reduce this to absurdity, but repair mechanisms can be overwhelmed by a number of different agents, isn't that correct?

DR. GEHRING: That is correct....

MR. WRIGHT: Just to summarize, is it fair to say that tissue levels of some agents may affect the metabolism of others by affecting one or more of these steps, including activation, deactivation, transport across membranes, repair, immune surveillance. Is that correct?

DR. GEHRING: By all means, as long as you include within that statement certain tissue levels.

(Tr. 5128-5133)

Gehring's animals were exposed to only one test agent at a time. Obviously, human beings are exposed to many agents.

DR. GEHRING: I do not really know how to caterorize. If you were working in a forest, for example, or as a farmer or whatever, and you are exposed in your natural enviroment, which you are, to this sea of carcinogens that surround us, now, is that occupational or isn't it?

MR. WRIGHT: Of course. But all of us are apparently exposed to a sea of carcinogens; we are exposed to a sea of enzyme inducers, enzyme repressors, a sea of chemicals which may compete for active sites, a sea of chemicals which may affect transport across cell membranes, all kinds of things, aren't we?

DR. GEHRING: That is life, yes.
(Tr. 5140-1)

Metabolism is also affected by genetics and the presence of disease:

MR. WRIGHT: Would you agree that there are some genetic factors which may affect the way human beings and other species metabolize particular compounds?

DR. GEHRING: Yes, absolutely.
(Tr. 5137)

MR. WRIGHT:....Let me ask you whether certain diseases, in particular liver disease, may affect the metabolism of a toxic chemical.

DR. GEHRING: It may, yes.

MR. WRIGHT: Thank you. I assume in these experiments you tried to use healthy animals.

DR. GEHRING: Yes.
(Tr. 5138)

In short, Dr. Gehring's experiments, elegant as they are, cannot possibly mimic the human experience. Dr. Gehring admits that multiple exposures, the presence of disease, and

genetic factors all influence the metabolism of toxic substances. But experimental animals are healthy, genetically homogenous, and are exposed to only one test agent at a time. Indeed, it is impossible to conceive of an experiment that would adequately reproduce the variability of exposures, disease states, and genetic factors found in any human population.

Gehring's proposal contains an even more serious flaw. His experiments are designed to elucidate the shape of the dose-response curve at its low-dose, low-response end. But much of the human population has already shifted above that portion of the curve

> MR. WRIGHT: The whole gist of your statement and your testimony is that it is necessary to overwhelm each of a number of protective mechanisms within the body, and let me use the word "overwhelm" in the Michaelis-Menton kinetical sense....before you produce any appreciable probability that an individual will develop cancer. That is correct?
>
> DR. GEHRING: With some materials that is correct, yes.
>
> MR. WRIGHT: Okay. What proportion of the human population develops cancer at some time in their lifetime?
>
> DR. GEHRING: Well, 25 percent develop cancer, about 20 percent die of cancer.
>
> MR. WRIGHT: Thank you. So certainly for those individuals, those successive steps have been overwhelmed, is that correct, in the Michaelis-Menton sense? ....for those individuals there has been some kind of overwhelming of each of those protective steps.
>
> DR. GEHRING: Yes, obviously, if it breaks out.
>
> (Tr. 5139-41)

8. Conclusion: Individual and Population Thresholds

The inadequacies of Dr. Gehring's models are shared by all threshold arguments. Suppose it were true that a given individual could not develop cancer unless his or her exposure reached a certain dose. Certainly that threshold would change with time depending on the individual's age, state of health, simultaneous exposure to other industrial and environmental agents, and a host of other factors. Even if we could determine that person's threshold today, it would be different tomorrow or next year. Different individuals have different genetic make-ups. Even if we could determine one person's threshold, it would not necessarily apply to anyone else. No two people have the same genetic constitution, state of health, and history of exposure to environmental, occupational, and dietary agents.

Furthermore, if there is an individual threshold, it is clear that a sizable fraction of the population exceeds it in their lifetime. As Dr. Mathew Meselson of Harvard put it:

> "As animals we humans are way past the threshold. We are like an experiment with mice or rats in which 25 percent of them are coming down with tumors. We are not a cancer-free population. We have an enormous incidence of cancer in our population. So that unless one is talking about a chemical which is being activated by an absolutely unique pathway unique to that chemical, an activating enzyme that does not work on anything else, or does something unique to the entity that no other chemical does, activates a mutagenic repair

> pathway that no other chemical does, unless that is the case, we are just talking about adding a little bit more when we talk about low dose, to what is already a lot, and demonstrably past the threshold, because we are already past any thresholds as a population."
>
> (Tr. 1545-46)

Dr. David Rall of NIEHS put it even more succinctly:

> "The threshold concept is presently inapplicable to the human population in the United States. Since 16% of our population now dies of cancer, I submit that as a population we have now exceeded any theoretical population threshold."
>
> (Tr. 354)

The threshold concept makes little sense when it is viewed in the context of the human population. The most eminent cancer experts in the world rejected the threshold concept and supported the logic of OSHA's proposal.[31] The threshold

---

[31] In general, see the written and oral testimony of Upton, Saffiotti, Rall, Selikoff, Nicholson, Weisburger, Kennedy, Peto, Bates, Squire, Holmberg, Stewart, and McCann. It should also be noted that some industry witnesses, in particular those charged with the day-to-day administration of industrial hygiene and occupational health in their companies, supported the "lowest feasible level" logic. For example, see the answer of Mr. William Janes of U. S. Steel, testifying for the American Iron and Steel Institute:

> MR. WRIGHT: Let's say if the company itself suspects a substance may be carcinogenic, has good evidence for believing that, is it in those circumstances appropriate to reduce the level of that carcinogen, suspected carcinogen to the lowest feasible level.
>
> MR. JANES: Good industrial hygiene practice would dictate that employee exposure should be reduced as much as possible.
>
> (Tr. 4630)